Oral delivery is the most patient-friendly mode of drug administration. Unfortunately, it is not possible for protein and other macromolecular drugs because the gastrointestinal tract is not permeable to undigested large molecules. Although many chemical permeation enhancers have been identified that improve the intestinal absorption of biologics, they often cause cytotoxicity or damage the intestinal mucosa. To address this issue, we sought to identify a permeation enhancer derived from fruits and vegetables, hypothesizing that the compounds found in natural foods would be well-tolerated by the gastrointestinal tract. Following a screen of over 100 fruits, vegetables, herbs, and fungi, we identified strawberry as a potent enhancer of macromolecular permeability both in vitro and in vivo. Natural product chemistry techniques revealed pelargonidin, an anthocyanidin, as the active compound in strawberry. In mice, pelargonidin enabled 100% bioactivity of oral insulin relative to the current gold standard of subcutaneous injection, without causing toxicity. These results underscore the potential of naturally derived compounds in biomedical applications and demonstrate pelargonidin as an especially potent new enhancer for the oral delivery of biologics.